

OBSTETRICS & GYNECOLOGY



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obgyn@greenjournal.org.

Date: Apr 11, 2019
To: "Robert M Rossi" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-407

RE: Manuscript Number ONG-19-407

Prenatal factors associated with failed induction of labor among obese women: developing a predictive model for failed induction of labor among obese women

Dear Dr. Rossi:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 02, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Abstract -

Objective: 1 in 4 women are obese, and obesity is associated with failed induction; aim was to evaluate antenatal risk factors associated with failed induction

Methods: population based cohort of obese women - BMI > 30 with induction between 2012-2016
 primary objective was to predict model probability failure from antenatal factors; multivariable logistic regression was then performed to find the association with antenatal factors

Results - of 19,844,580 births, 1,098,981 were obese women undergoing induction of labor. 24.9% were unsuccessful, 16 variables were evaluated and a discriminatory model with AUC 0.79 was developed

Conclusion - risk of failed induction with obesity
 predictive model with AUC of 0.79 was developed

Introduction - obesity affects 39.8% of population and is a known risk factor for obstetric complications. WHO class III obese patients and those with previous c-sections have an increased risk of failed induction, also WHO III has increased risk of atony and PPH with vaginal delivery as compared to c/s, goal was to create a predictive model for risk factors for failed induction

primary objective - predictive model for failed induction

secondary outcome - strength of association for risk factors with failure

Methods - population based retrospective cohort singleton pregnancies with BMI >30 kg/m² from NCHS database and US livebirth records

Factors in model - 1) maternal demographics - age, race, cigarette smoking, socioeconomic status

2) maternal co-morbidities - DM, CHTN, pregnancy induced HTN

3) obstetrical factors - hx of c/s, hx NSVD, LGA, SGA, maternal height, weight gain, weight, parity
 birthweight was used as a surrogate for EFW

statistics are described

Results - 1,098,981 obese women underwent IOL - 24.9% failed

class I, II, and III failure rates are: 22.1, 25.5, and 31.6%

obese women with failed induction are more likely to be: AMA, black diabetic, BMI is higher, height is lower, previous c-section, primiparous, longer interpregnancy interval, higher birth weight

failed induction patients have a higher rate of adverse outcomes and neonatal complications

Discussion - obesity rate is 23%, failed induction is 24.9% in obese versus 17% in nonobese
 a model would help plan staffing
 limitations - retrospective data, no info on abnormal fetal status or Bishop's score

Comments - While I agree that a model would be helpful for counseling patients, a lot of this data is not new - these risk factors for failure to achieve vaginal delivery are known, so just the model and its utility is new
 the concerns I would like to see addressed, and to know how these influence the data are as follows:
 There is no documentation of a uniform induction protocol, so it is hard to know what constituted a failed induction - just how hard did they try with the inductions or did they try very little. There is no data and the answer is likely highly variable, so this could affect the results - please address this

there is also no measurement of a Bishop's score, so there could be significant variability in the starting point of various patients

Is it known if these were truly "failed inductions" or were they just "failure to obtain vaginal deliveries" - were the c-sections for failure of induction or need of c-section because of various obstetrical indications - failed induction, AOD, APA, NRFS, etc

I also have concerns about tables 1 and 2 - most of the p values are < 0.001 but when looking at the numbers, they are often almost the same, so it is hard to believe there is truly a statistically significant difference - the statistics would need to be reviewed

Reviewer #2: The authors developed a model for predicting failed induction of labor for women with prepregnancy obesity. Their data were derived from 1.1 million singleton births to obese women meeting entry/exclusion criteria.

1. Line 93: It would seem more accurate to rephrase this sentence to the effect that, "Approximately one in four obese parturients who undergo induction of labor will not succeed in delivering vaginally."
2. Line 101: It seems prudent to note here that the model was constructed for singleton pregnancies.
3. Lines 110-12: In the construction of this model, were operative vaginal deliveries (i.e. forceps, vacuum) considered with those delivering vaginally or by cesarean delivery? How were failed attempts at vaginal operative delivery classified? Please clarify.
4. Line 117: It seems pertinent to mention the rate of obesity in reproductive age women, not just the general population.
5. Line 137: Do the authors mean, "...is likely attributable to variable distribution of maternal, obstetric, and fetal factors..."?
6. Lines 146-7: For clarity, would the authors consider substituting "...prior to attempted induction of labor." For "...prior to delivery..."?
7. Lines 165-7: Other maternal morbidities which seem pertinent include cardiovascular disease, autoimmune disease, and chronic kidney disease. Were these evaluated as potential predictors?
8. Line 167: Not only treating prior cesareans as a dichotomous variable but also analyzing number and type (low transverse versus vertical) of prior cesareans as well as prior failed inductions of labor seem pertinent as predictors. Is this information available from the database?
9. Line 165: Gestational diabetes is enumerated in Table 1 and should also be mentioned as a maternal co-morbidity in the text.
10. Lines 167-74: The authors used actual birth weight data as a surrogate for estimated fetal weight in their prediction model of induction of labor failure. The problem with doing this is that there is little concordance between (sonographic as well as hands-on) estimates of fetal weight and actual birth weight. This is of particular concern for obese pregnant women, for whom the sensitivity and positive predictive values for sonographically estimated fetal weight (SEFW) is poor (cf, e.g. Samuelli. Arch Gynecol Obstet 2019;299:97-103) and for whom the inaccuracy of SEFW increases with increasing maternal BMI and gestational age (cf, e.g. Paganelli. Arch Gynecol Obstet 2016;293:775-81). Perhaps the authors can develop a variable based on the range of actual birth weight for EFW as a predictor for failed induction of labor which is compatible with actual clinical practice.
11. Lines 201-2: Are the differences among these three percentages statistically significant?
12. Line 204: Infertility treatment is mentioned here and in Table 1 and should also be mentioned in the Methods among

the prediction factors considered.

13. Line 212: Interpregnancy interval is mentioned here and in Table 2 and should also be mentioned in the Methods among the prediction factors considered.

14. Line 228: Parity was selected as a significant variable in the multivariable analysis (Table 5) but is not listed in

15. Box 1. Please clarify.

16. Line 231: The text states that gestational diabetes was selected as a significant factor, yet it appears in neither

17. Table 5 nor Box 1. Please clarify.

18. Line 242: Please provide a citation for the 17.2% figure.

19. Line 265: In the interest of transparency it may also be noted that foreknowledge of the likelihood of failure of induction might bias the provider towards earlier operative intervention in an induction of labor.

20. Lines 284-6: Although the authors' intent is to apply this model prior to admission for delivery there is nothing that precludes its utilization at the time of admission. At this point inclusion of the Bishop score would seem a viable consideration.

21. Table 1: How was maternal weight at delivery determined? Do all the hospitals from which data was accumulated weigh patients at the time of admission for delivery?

22. Tables 1-5: All the title lines include the words, "...failed induction of labor". However, the columns below are labeled "Failed IOL" and "Successful IOL". Suggest removing the word "failed" from the title lines.

23. Figure 1: It might be interesting to report the vaginal and cesarean delivery rates for the 2,725,070 non-excluded obese women who did not undergo induction as a means of assessing the role of labor induction in determining route of delivery in this population.

24. Figure 2: It may be of interest to insert value(s) at point(s) on this ROC curve to indicate at which values the combination of true positive and false positive rate were greatest.

Reviewer #3: REVIEWER COMMENTS: ONG-19-407

Title: The title is appropriate for the review, however could be shortened to be less redundant.

Summary:

This is a retrospective population based cohort study evaluating prenatal factors associated with obesity to develop a predictive model that could be used to help predict the risk of failed induction among obese women.

Abstract:

1. The first two sentences of the objective should have a reference and perhaps be moved to the introduction.

2. Lines 95-97: The last sentence of the objective section of the abstract is appropriate.

3. The methods section (lines 98-104) does not explain where the data came (which database) from and how it was reviewed. Consider including inclusion criteria in this section.

4. The results section (lines 104-108) does not report which 16 variables were included in the model and how they came to the conclusion that these were the best variables to include in the model.

5. The conclusion (lines 109-114): This conclusion cannot be made without a validation test. This model only uses historical data to come up with the predictive model but does not do any actual validation testing on a hold out sample or prospective cohort.

Introduction:

6. The background introduction is appropriate but very general.

7. Lines 124-129: While it gives us the physiologic reason as to why failed inductions are more likely in obese women, it does not provide background data on which specific additional variables in conjunction with obesity could increase an obese women's risk of having a failed induction. Lines 136-138 is a very general statement that does not specify which maternal, fetal or obstetric factors can increase the risk of failed induction, nor does it provide the reader supporting evidence that these variables uniquely increase the risk of failed induction among obese women who are being induced.

Materials and Methods:

8. Line 153: What does NCHS stand for? It is not previously defined. How did you glean the inductions from this database since they do not explicitly document women undergoing labor induction? Were induction of labor and augmentation of labor differentiated since the database includes both? Why was this database selected over others?

9. Lines 162-170: Were these the factors evaluated or were these the final factors included in the final model? If the latter, which factors were evaluated prior to determining what to include in the final model? Was method of induction considered in the analysis? Was any adjustment performed for epidural use, method of induction, or indication for cesarean?

10. Could differentiating methods of induction in different states/hospitals have affect the outcomes?

11. What defined a failed induction? Were all cesareans assessed due to failed inductions or were there other indications for cesareans included in the analysis?

12. Lines 171-173: Can you provide evidence that prenatal ultrasound based estimated fetal weight is a good predictor of actual birth weight in obese women? Among obese women, is there any evidence that prenatal EFW>90% is associated with increased risk of failed induction and cesarean?

13. Lines 178: Why were women with labor inductions past 42 weeks included in the model ? Why were women between 34-37 weeks not included in the model?

14. Lines 180-194: Statistical analysis: Model validation

15. Both stepwise backward selection and ROC curve analyses was used for the model validation.

16. Were out time validation tests with the years 2017-2018 considered or any validation testing performed?

17. With a large the sample data as that of the NCHS, it may be been beneficial to divide the sample into training and test datasets. The latter may help with validating and verifying the accuracy of the model's output and decrease the risk of overfitting the model.

18. Line 202: Was the association between pre-pregnancy BMI and risk of failed induction among all women undergoing induction of labor assessed or was risk assessed for obese women only? If pre-pregnancy BMI is predictive of likelihood of failed induction rates, was pre-pregnancy BMI evaluated in the predictive model?

Results:

19. Line 198: How was the mother's pre-pregnancy BMI ascertained in the database? Was the pre-pregnancy BMI assessed as a predictive variable in the model? If not, please explain.

20. Line 201: How was failed induction of labor defined in this analysis? Were all indications for cesarean deliveries due to failed inductions?

21. Lines 216-224: What is the relevance of this data with regard to developing a predictive model for failed induction rates among obese women?

22. Was validation testing performed?

Discussion:

Lines 241-242:

23. The "failed IOL" percentage should be clarified because obese women are more likely to have preeclampsia, IUGR and consequently non-reassuring tracing, all of which could lead to cesarean sections one way or another, and may not necessarily be due to failed induction of labor.

24. Lines 244-246: Discrimination and calibration were both performed in the analysis, but no validation testing using sample data was performed. Please explain.

25. The limitations section of the discussion is well written and delineates well the pitfalls associated with this model.

26. Table 2: symbol used with total previous births implies a median was calculated, however a mean and SD are reported, please clarify.
27. Table 3: Please clarify what *No prior history of cesarean delivery is referring to. The symbol is not used in the table.
28. Table 5: please correct the legend. None of the symbols in the legend are used in the table; please clarify what the odds ratio were adjusted for in the multivariable logistic regression

STATISTICAL EDITOR'S COMMENTS:

1. General: The model coefficients are cited to a degree of precision not supported by the data samples. The coefficients are cited to 6 or 7 significant figures, while the number of adverse events was ~ 270,000 total and much fewer for many subsets. These should be rounded to 5 or 6 figures at most. The notable smaller samples (with therefore less precision) apply to prior CD, chronic HTN, pre-existing DM, gestational HTN, LGA, BW > 4.5 kg, SGA, cigarette smoker, most of which had adverse counts in the 6 to 20 K range, hence coefficients to the nearest 1 part per million or per 10 million are not supported.
2. Furthermore, Fig 1, there were missing data re: pre-pregnancy BMI on 1.7 million of the original cohort, which contributes to the uncertainty of the estimates. These data are obviously only re: those women who (1) underwent IOL and (2) were obese. If different standards or protocols or clinical judgement were a part of the decision as to which women underwent IOL, then this analysis only pertains to that subset, not to all obese women who potentially could be candidates for IOL.
3. Should amend the presentation of the multivariable model to include an analysis of how much each variable in the final model contributed to variance reduction. For instance, by ranking them in order of importance, or showing how much the model's predictive ability was diminished by reduction of each variable from the final model.
4. Figs 2 and 3: These convey important information re: (1) the overall concordance of the model with outcome of failed IOL and (2) the relative size of the samples along the spectrum of increasing probability of failed IOL, but the picture is incomplete. Need to emulate fig 8 from "Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): Explanation and Elaboration" by K.G.M. Moons, D.G. Altman, J.B. Reitsma, J.P.A. Ionnidis, P. Macaskill, E.W. Steyerberg, A.J. Vickers, D. F. Ransohoff and G. S. Collins, *Annals of Internal Medicine* 2015; 162:W1-W73.
5. This figure allows the reader to see the relationship of observed vs predicted probabilities along the spectrum of probabilities from the data, along with confidence intervals for those prediction estimates. An added feature is the display below the x-axis of the relative counts of adverse vs non-adverse outcomes. Alternatively, those could be displayed (similar to survival analysis graphs), with numerical counts of adverse vs non-adverse outcomes at the intervals referred by the graph, or in the case of a large series like the present study, as a Table (could be supplemental). The advantage to this level of detail is that it would convey to the reader the strength of association at various model scores, along with their relative uncertainty, reflecting how many data were available at various cut-points. There are sufficient data to have twenty strata, as the Authors show in Fig 3.
6. The supplemental digital calculator provides a specific probability (according to several inputs I tried), to the nearest .01%. This is an unrealistic level of precision. Instead, should give a point estimate (at most to nearest .1%), then include the 95% CIs for the 5% increment outlined in Fig 3 which contains the point estimate.
7. Additional limitations include the lack of a sample to validate the model, since all data were used to construct the model.

Associate Editor's Comments:

We would be happy to consider a revised manuscript but our general feeling was that a model with 16 inputs would be clinically unwieldy and would like to see a more parsimonious model. Also, give the imprecision of fetal weight estimation, the model input of actual birth weight is not appropriate and should be removed.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
 1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
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2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

5. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

9. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

10. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

11. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the

editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

12. The Journal's Production Editor had the following to say about the figures in your manuscript:

"FIGURE 3: missing y-axis label"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

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If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 02, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

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